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High Levels of Serum Uric Acid Predict Severity of Coronary Artery Disease in Patients with Acute Coronary Syndrome

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Abstract

We aimed to elucidate the relation between serum uric acid (SUA) level and severity of coronary artery disease (CAD) in nondiabetic, nonhypertensive patients (n = 246) with acute coronary syndrome (ACS). Severity of CAD was assessed by the Gensini score. One, 2, and 3 or more diseased vessels were identified in 87 (35.4%), 55 (22.4%), and 104 (42.2%) patients, respectively. Patients with hyperuricemia had higher Gensini score, high number of diseased vessels, critical lesions, and total occlusion. Serum uric acid level was significantly associated with number of diseased vessels. Serum uric acid was an independent risk factor for multivessel disease by univariate analysis. High levels of SUA associated with the severity of CAD in nondiabetic, nonhypertensive patients with ACS.

Keywords

serum uric acid, Gensini score, acute coronary syndrome

Introduction

Hyperuricemia is frequently noted in patients with coronary artery disease (CAD), and increased serum uric acid (SUA) was associated with increased risk of adverse cardiovascular outcomes in patients with CAD.[1-4] The physiopathological mechanisms leading to increased risk are still unknown, but SUA has been significantly associated with endothelial dysfunction, antiproliferative effects, and high oxidative stress.[5,6] Severity of CAD may clarify the relation between SUA and adverse outcomes in CAD. The aim of this study was to elucidate the relation between SUA level on admission and severity of CAD in nondiabetic, nonhypertensive patients with acute coronary syndrome (ACS).

Methods

Patients

The study involved 465 consecutive patients admitted to our hospital with ACS. Patients with a history of diabetes mellitus, defined as a fasting blood glucose level >110 mg/dL or using antidiabetic drugs, a history of hypertension, defined as blood pressure of ≥140/90 mm Hg or taking antihypertensive medication, a history of renal disease (or serum creatinine level >1.5 mg/dL), a history of coronary intervention or coronary artery bypass graft, and history or presence of heart failure were excluded.

Finally, 246 patients were included in the study. Informed consent was obtained from all patients. Patients were divided into 2 groups according to SUA levels as normouricemic or hyperuricemic. The study was approved by our local ethical committee. All demographic and clinical data were collected prospectively.

Laboratory Analysis

In all cases, the blood samples including SUA, glucose, blood urea nitrogen, creatinine, and lipid profile were obtained after

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Table 1. Association of Atherosclerotic Characteristics of Patients and Hyperuricemia

	Normouricemic Patients (n = 152)	Hyperuricemic Patients (n = 94)	*P*
Gensini score	6 (2-16)	10 (3-28)	<.001
Number of diseased vessel	1.8 ± 0.8	2.5 ± 0.7	<.001
Number of diseased vessel (>50%)	1.4 ± 0.6	2.1 ± 0.7	.011
Number of critical lessions (>50%)	1.8 ± 1	3.3 ± 1.9	<.001
Number of critical lessions (>70%)	1.6 ± 0.9	2.9 ± 1.6	<.001
Number of non-critical lessions	0 (0-6)	1 (0-6)	.038
Totally occlusion (n, %)	76 (50%)	57 (60.6%)	.022
Left main disease (n, %)	3 (1.9%)	3 (3.1%)	.548
1 Vessel (n, %)	71 (46.7%)	16 (17.0%)	
2 Vessels (n, %)	41 (26.9%)	14 (14.8%)	<.001
3 or more vessels (n, %)	40 (26.3%)	64 (68.0%)	

fasting overnight (Thermo clinical lab system with Konelab 60 I kits, Helsinki, Finland). Hyperuricemia was defined as SUA > 6.0 for women and >6.5 mg/dL for men.[7,8]

Coronary Angiography

Quantitative coronary angiography was performed by 2 experienced interventional cardiologists (M.D. and M.G.K.) by the Judkins technique; they had no knowledge of the clinical information. The Gensini score was used to evaluate the severity of atherosclerosis.[9] The most severe stenosis in each of 8 coronary segments (left anterior descending artery, main diagonal branch, first septal perforator, left circumflex artery, obtuse marginal and posterolateral vessels, right coronary artery, and main descending branch) was graded from 1 to 4 (1%-49% lumen diameter reduction: 1 point, 50%-74% stenosis: 2, 75%-99% stenosis: 3, 100% occlusion: 4) to give a total score of between 0 and 32.

Statistical Analysis

All analyses were performed using SPSS V 16.0 for windows (version 16.0, SPSS, Chicago, Illinois). Quantitative variables were expressed as mean value ± standard deviation for parametric variables and median and range for nonparametric variables. Comparison of parametric values between 2 groups was performed by means of the independent samples *t* test. Comparison of nonparametric values between 2 groups was performed by the Mann–Whitney *U* test. Categorical variables were compared by the chi-squared test. The Pearson test was used to assess correlation of parametric variables and the Spearman used test for nonparametric variables. Differences among number of diseased vessel groups were tested with 1-way analysis of variance. Multivariate logistic regression analysis was performed to assess the effects of systolic and diastolic blood pressure, uric acid, age, gender, total cholesterol, and white blood cell on severity of CAD. A 2-tailed $P < .05$ was considered significant.

Results

Hyperuricemia was determined in 94 (38.2%) patients. One, 2, and 3 and more diseased vessels were determined in 87 (35.4%), 55 (22.4%), and 104 (42.2%) patients, respectively. Table 1 presents the association of atherosclerotic properties of patients and hyperuricemia. Patients with hyperuricemia had higher Gensini score, high number of diseased vessels, critical lesions >50% or >70% and totally occlusion. Serum uric acid level was significantly associated with number of diseased vessels. Only advanced age and high low-density lipoprotein cholesterol (LDL-C) level were associated with number of diseased vessels (Table 2).

Serum uric acid was an independent risk factor for multivessel disease by univariate analysis (odds ratio [OR]: 1.47, $P < .001$). Gensini score was correlated with SUA ($r = .452$, $P < .001$), age ($r = .452$, $P = .001$), creatinine level ($r = .151$, $P = .019$), and LDL-C ($r = .165$, $P = .012$). Number of diseased vessels correlated with SUA ($r = .334$, $P < .001$), age ($r = .171$, $P = .011$), and LDL-C ($r = 178$, $P = .007$).

After multivariate analysis, high levels of SUA were independent predictors of multivessel CAD (OR: 1.616, 95% confidence interval 1.243-2.101, $P < .001$) together with age (OR: 1.043, 95% confidence interval 1.008-1.078, $P = .014$).

Discussion

Because of the effects of SUA to atherogenesis,[10] we hypothesized that in nondiabetic, nonhypertensive patients with ACS, high level of SUA was associated with the severity of CAD. We found that high levels of SUA were significantly associated with severity of CAD in these patients with ACS.

In some epidemiological studies, a high level of SUA was an independent risk factor for atherosclerosis, cerebro- and cardiovascular events, cardiovascular mortality, and all-cause mortality in patients with CAD and in the general population.[1-4,11,12] In a recent meta-analysis, investigators reported that hyperuricemia was associated with an increased risk of CAD incidence and mortality.[13] Despite the strength of

Table 2. Baseline Clinical Characteristics of the Study Population According to the Angiographic Findings

	1 Vessel (n = 87)	2 Vessels (n = 55)	≥3 Vessels (n = 104)	P
Uric acid, mg/dL	5.3 (2.7-9.5)	5.6 (2.9-9.5)	6.7 (3.1-12.5)	<.001
Gensini score	4 (2-7)	7 (3-11)	11 (5-28)	<.001
Age, years	55 ± 11	55 ± 13	60 ± 12	.017
Systolic BP, mm Hg	113 (90-140)	110 (85-140)	116 (90-140)	.084
Diastolic BP, mm Hg	71 (60-90)	72 (60-90)	72 (50-90)	.846
BMI, kg/m^2	28.4 (23-36)	26.4 (22-35)	26.5 (20-34)	.071
Hemoglobin, mg/dL	14.4 (8.9-18.5)	14.5 (8.1-19)	14.2 (9.4-18)	.624
White blood cell, mm^3	10.1 (3.6-19.5)	10.5 (4.7-20)	11 (1.6-20.8)	.516
Glucose, mg/dL	97 ± 12	101 ± 12	99 ± 14	.280
BUN, mg/dL	25 (8-56)	26 (8-70)	26 (5-72)	.879
Creatinine, mg/dL	0.8 (0.3-1.3)	0.9 (0.3-1.4)	0.9 (0.2-1.5)	.106
Sodium, mmol/L	139 ± 3.3	139 ± 3.5	139 ± 2.6	.343
Potassium, mmol/L	4.2 ± 0.3	4.2 ± 0.4	4.1 ± 0.4	.814
Total cholesterol, mg/dL	176 ± 34	186 ± 42	188 ± 42	.129
LDL-C, mg/dL	110 ± 33	120 ± 39	124 ± 35	.043
HDL-C, mg/dL	37 (20-88)	33 (21-57)	36 (19-79)	.103
Triglycerides, mg/dL	145 (32-849)	158 (51-650)	140 (33-675)	.625
Total protein, g/dL	6.6 ± 0.5	6.6 ± 0.5	6.6 ± 0.6	.861
Albumin, g/dL	4 ± 0.4	3.9 ± 0.4	3.9 ± 0.5	.644

Abbreviations: BP, blood pressure; BMI, body mass index; BUN, blood urea nitrogen; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol.

these associations between SUA and CAD, controversial findings were obtained by others.[14,15] So, the role of SUA as an independent risk factor for cardiovascular events remains uncertain.

The underlying mechanisms linking SUA and cardiovascular mortality have not yet been clearly demonstrated. Uric acid is the final product of purine metabolism.[16] Although it has antioxidant properties at low serum levels, when this value is above 6 to 6.5 mg/dL (for females and males, respectively), these properties change to a pro-oxidant state.[7,8] Uric acid plays an important role in the formation of free radicals, platelet adhesiveness, and aggregation as well as thrombus formation.[5,13,17,18] High levels of SUA was associated with endothelial dysfunction, antiproliferative effects, impaired nitric oxide production, lipid peroxidation, and smooth muscle proliferation.[3,6,13,19-21] Kanbay et al suggested that hyperuricemia may also cause microvascular damage in the renal vascular bed and exacerbate vascular disease.[19] We suggested that high SUA levels are associated with severity of CAD and this may explain the cardiovascular outcomes associated with increased SUA levels.

A positive association between SUA level and presence of CAD was reported in previous studies.[22,23] However, the results of studies investigated a relation between SUA level and severity of CAD was controversial.[24-27] The study populations in these studies were different from each other and some of them had small sample sizes. Deveci et al reported that SUA was associated with the presence and severity of CAD in patients who underwent coronary angiography.[24] Kanbay et al showed that SUA was an independent determinant of severity of CAD in patients with mild-to-moderate chronic kidney disease.[25] Lu et al reported that there was no relationship between SUA levels and the severity of CAD.[26] Gur et al showed that SUA correlated with the presence, but not the severity of CAD.[27] In our study, first we showed this relationship in patients with ACS who were nonhypertensive, nondiabetic, and had normal kidney function. Also, our study group did not take any antihypertensive agents that may affect SUA levels (eg, diuretics).[28] So, our results showed an effect of SUA on severity of CAD without confounding by these factors.

Elevated SUA has been found to be associated with disordered glucose metabolism, dyslipidemia, obesity, metabolic syndrome, hypertension, and renal disease each of which play a role in the pathogenesis of CAD.[15,29-31] Because of this association, we excluded patients with diabetes, hypertension, renal disease, and history of past coronary intervention. Also, the characteristics of patients with hyperuricemia were not significantly different from patients with normouricemia (Table 3). A link between elevated SUA levels, nonalcoholic fatty liver disease, and vascular risk has been also suggested.[32] In our study, SUA levels were not associated with liver function tests.

Serum uric acid may be an important, simple and cost effective vascular risk marker which is routinely measured in clinical practice.[33]

Limitations

We assessed the severity of coronary atherosclerosis with Gensini score and number of diseased vessels. The SYNTAX score is an angiographic tool to determine the complexity of CAD.[34] It provides more detailed information about coronary atherosclerosis rather than the Gensini score. However, we did not use SYNTAX score because when we designed the study, the SYNTAX score was not used consistently. Also investigators previously reported an association between a fall in SUA levels

Table 3. Clinical Characteristics of the Patients

	Normouricemic Patients (n = 152)	Hyperuricemic Patients (n = 94)	*P*
Uric acid, mg/dL	5.1 (2.7-6.3)	7.1 (6.4-12.5)	<.001
Age, years	56 ± 12	59 ± 12	.170
Gender (male, %)	123 (80%)	80 (85%)	.401
Smoking (n, %)	91 (59%)	60 (63%)	.535
BMI, kg/m^2	26.4 (21-35)	28 (20-36)	.279
Hemoglobin, mg/dL	14.5 (8.1-18.5)	14.8 (9.6-19)	.047
Glucose, mg/dL	98 ± 12	100 ± 14	.281
BUN, mg/dL	25.5 (5-70)	22 (8-72)	.142
Creatinine, mg/dL	0.9 (0.2-1.4)	1 (0.3-1.5)	.002
Total cholesterol, mg/dL	183 ± 38	184 ± 42	.913
LDL-C, mg/dL	118 ± 35	119 ± 36	.865
HDL-C, mg/dL	35 (19-88)	33 (20-79)	.257
Triglycerides, mg/dL	120 (32-661)	120 (33-849)	.790
USAP (n, %)	34 (22.4%)	21 (22.3%)	.953
Non-STEMI (n, %)	59 (38.8%)	35 (37.2%)	.743
STEMI (n, %)	59 (38.8%)	38 (40.5%)	.782

Abbreviations: BMI, body mass index; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; USAP, unstable angina pectoris; STEMI, ST-elevation myocardial infarction.

and statin use[35] but we had no information about statin use in our study.

We showed that high levels of SUA are associated with the severity of CAD in nondiabetic, nonhypertensive patients with ACS. This may explain the cardiovascular risk associated with raised SUA levels. High levels of SUA may become surrogate markers of CAD severity.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: The authors declare the absence of any commercial or other associations that might pose a conflict of interest.

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References

1. Okura T, Higaki J, Kurata M, et al. Japanese coronary artery disease study investigators. Elevated serum uric acid is an independent predictor for cardiovascular events in patients with severe coronary artery stenosis: subanalysis of the Japanese Coronary Artery Disease (JCAD) Study. *Circ J*. 2009;73(5):885-891.
2. Meisinger C, Koenig W, Baumert J, Döring A. Uric acid levels are associated with all-cause and cardiovascular disease mortality independent of systemic inflammation in men from the general population. The MONICA/KORA cohort study. *Arterioscler Thromb Vasc Biol*. 2008;28(6):1186-1192.
3. Karagiannis A, Mikhailidis DP, Tziomalos K, et al. Serum uric acid as an independent predictor of early death after acute stroke. *Circ J*. 2007;71(7):1120-1127.
4. Høieggen A, Alderman MH, Kjeldsen SE, et al. The impact of serum uric acid on cardiovascular outcomes in the LIFE study. *Kidney Int*. 2004;65(3):1041-1049.
5. Vasquez-Vivar J, Santos AM, Junqueira VB, Augusto O. Peroxynitrite-mediated formation of free radicals in human plasma: EPR detection of ascorbyl, albumin-thiyl and uric acid-derived free radicals. *Biochem J*. 1996;314(pt 3):869-876.
6. Anker SD, Leyva F, Poole-Wilson PA, Kox WJ, Stevenson JC, Coats AJ. Relation between serum uric acid and lower limb blood flow in patients with chronic heart failure. *Heart*. 1997; 78(1):39-43.
7. Naghavi M, John R, Naguib S, et al. pH heterogeneity of human and rabbit atherosclerotic plaques; a new insight into detection of vulnerable plaque. *Atherosclerosis*. 2002;164(1):27-35.
8. Khosla UM, Zharikov S, Finch JL, et al. Hyperuricemia induces endothelial dysfunction. *Kidney Int*. 2005;67(5):1739-1742.
9. Gensini GG. A more meaningful scoring system for determining the severity of coronary heart disease. *Am J Cardiol*. 1983;51(3): 606-607.
10. Kanellis J, Watanabe S, Li JH, et al. Uric acid stimulates monocyte chemoattractant protein-1 production in vascular smooth muscle cells via mitogen-activated protein kinase and cyclooxygenase-2. *Hypertension*. 2003;41(6):1287-1293.
11. Krishnan E, Pandya BJ, Chung L, Dabbous O. Hyperuricemia and the risk for subclinical coronary atherosclerosis—data from a prospective observational cohort study. *Arthritis Res Ther*. 2011;13(2):R66.
12. Chen JH, Chuang SY, Chen HJ, Yeh WT, Pan WH. Serum uric acid level as an independent risk factor for all-cause, cardiovascular, and ischemic stroke mortality: a Chinese cohort study. *Arthritis Rheum*. 2009;61(2):225-232.
13. Kim SY, Guevara JP, Kim KM, Choi HK, Heitjan DF, Albert DA. Hyperuricemia and coronary heart disease: a systematic review and meta-analysis. *Arthritis Care Res*. 2010;62(2):170-180.
14. Waring WS, Adwani SH, Breukels O, Webb DJ, Maxwell SR. Hyperuricaemia does not impair cardiovascular function in healthy adults. *Heart*. 2004;90(2):155-159.
15. Tsai TH, Chen YL, Chen SM, et al. Uric acid is not an independent predictor of cardiovascular death in patients with angiographically proven coronary artery disease. *Chang Gung Med J*. 2009;32(6):605-613.
16. Gagliardi AC, Miname MH, Santos RD. Uric acid: a marker of increased cardiovascular risk. *Atherosclerosis*. 2009;202(1):11-17.
17. Kanellis J, Kang DH. Uric acid as a mediator of endothelial dysfunction, inflammation, and vascular disease. *Semin Nephrol*. 2005;25(1):39-42.
18. Johnson R, Kang D, Feig D, et al. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? *Hypertension*. 2003;41(6):1183-1189.
19. Kanbay M, Sánchez-Losada LG, Franco M, et al. Microvascular disease and its role in the brain and cardiovascular system: a potential role for uric acid as a cardiorenal toxin. *Nephrol Dial Transplant*. 2011;26(2):430-437.
20. Dawson J, Walters M. Uric acid and xanthine oxidase: future therapeutic targets in the prevention of cardiovascular disease? *Br J Clin Pharmacol*. 2006;62(6):633-644.

21. Tavil Y, Kaya MG, Oktar SO, et al. Uric acid level and its association with carotid intima-media thickness in patients with hypertension. *Atherosclerosis*. 2008;197:159-163.
22. Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. *N Engl J Med*. 2008;359(17):1811-1821.
23. Niskanen L, Laaksonen DE, Lindstrom J, et al. Serum uric acid as a harbinger of metabolic outcome in subjects with impaired glucose tolerance: the Finnish diabetes prevention study. *Diabetes Care*. 2006;29(3):709-711.
24. Deveci OS, Kabakci G, Okutucu S, et al. The association between serum uric acid level and coronary artery disease. *Int J Clin Pract*. 2010;64(7):900-907.
25. Kanbay M, Ikizek M, Solak Y, et al. Uric acid and pentraxin-3 levels are independently associated with coronary artery disease risk in patients with stage 2 and 3 kidney disease. *Am J Nephrol*. 2011;33(4):325-331.
26. Lu P, Hu D, Lu J, Wang W, Chen B. The association between uric acid and coronary heart disease. *Zhonghua Nei Ke Za Zhi*. 2002; 41(8):526-529.
27. Gur M, Yilmaz R, Demirbag R, Aksoy N. Relation of serum uric acid levels with the presence and severity of angiographic coronary artery disease. *Angiology*. 2008;59(2):166-171.
28. Daskalopoulou SS, Tzovaras V, Mikhailidis DP, Elisaf M. Effect on serum uric acid levels of drugs prescribed for indications other than treating hyperuricaemia. *Curr Pharm Des*. 2005; 11(32):4161-4175.
29. Jelic-Ivanic Z, Memon L, Spasojevic-Kalimanovska V, Bogavac-Stanojevic N, Spasic S. Independent association of high serum uric acid concentration with angiographically defined coronary artery disease. *Tohoku J Exp Med*. 2007;211(4): 369-377.
30. Vaziri ND, Freel RK, Hatch M. Effect of chronic experimental renal insufficiency on urate metabolism. *J Am Soc Nephrol*. 1995;6(4):1313-1317.
31. Athyros VG, Karagiannis A, Ganotakis ES, et al. Association between the changes in renal function and serum uric acid levels during multifactorial intervention and clinical outcome in patients with metabolic syndrome. A post hoc analysis of the ATTEMPT study. *Curr Med Res Opin*. 2011;27(8):1659-1668.
32. Katsiki N, Athyros VG, Karagiannis A, Mikhailidis DP. Hyperuricaemia and Non-Alcoholic Fatty Liver Disease (NAFLD): a relationship with implications for vascular risk? *Curr Vasc Pharmacol*. 2011 Sep 22;9(6):698-705.
33. Strasak A, Ruttmann E, Brant L, et al. Serum uric acid and risk of cardiovascular mortality: a prospective long-term study of 83,683 Austrian men. *Clin Chem*. 2008;54(2):273-284.
34. Serruys PW, Onuma Y, Garg S, et al. Assessment of the SYNTAX score in the syntax study. *EuroIntervention*. 2009; 5(1):50-56.
35. Athyros VG, Mikhailidis DP, Liberopoulos EN, et al. Effect of statin treatment on renal function and serum uric acid levels and their relation to vascular events in patients with coronary heart disease and metabolic syndrome: a subgroup analysis of the GREek Atorvastatin and Coronary heart disease Evaluation (GREACE) Study. *Nephrol Dial Transplant*. 2007;22(1):118-127.